

U.S.S.N. 08/924,994

Filed: September 5, 1998

AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

22. (New) The method of claim 20 comprising quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease by reacting a saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof, and

correlating the levels of at least one apolipoprotein in the saliva with the levels in serum associated with the presence of lipid disorders or risk of cardiovascular disease.

23. (New) The method of claim 20 wherein the measurements of the apolipoproteins in serum are normalized against the level of albumin in the saliva as compared to the level of albumin in serum from the individual.

Remarks

The Abstract

The abstract has been amended to delete the reference to an issued U.S. Patent.

Rejection Under 35 U.S.C. § 112

Claims 1-20 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 has been amended to recite a detection and correlation step. However, MPEP § 2172.01 states that "[a] claim which omits matter disclosed to be essential to the invention as described in the specification or in other statements of record may be rejected under 35 U.S.C. 112, first paragraph, as not enabling... Such essential matter may include missing elements, steps

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or necessary structural cooperative relationships of elements described by the applicant(s) described by the applicant(s) as necessary to practice the invention."

Claim 4 has been amended to correct the spelling of "label".

Claim 6 has been amended to specifically recite "remove mucopolysacchrides from the saliva".

The Applicants respectfully traverse the rejection of claim 7 as allegedly failing to specifically define what is being encompassed by the term "stimulation" as recited in the claim. The term "stimulation" as used in the context of "saliva is collected after stimulation" in claim 7 is well defined and explained in the specification. (See, e.g., p. 18, lines 7-12) Moreover, "saliva is collected after stimulation" would be well understood by one of ordinary skill in the art. (See, e.g., the references cited in p. 4, lines 1-4).

The Applicants respectfully traverse the rejection to claim 8 as allegedly omitting essential elements. One of ordinary skill in the art would know how to determine the level of albumin. Albumin levels are routinely assayed using clinically and commercially available reagent kits, for example, obtainable from Sigma. It is not important how the levels are measured, as long as the levels in both the saliva and the patient's serum are measured, and the relative concentrations normalized.

Claim 9 has been amended to correct antecedent basis and to insert where the saliva and serum in which the apolipoproteins are measured are obtained from.

Mucopolysaccharides has been made plural in claim 13.

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The Applicants respectfully traverse the rejection to claim 12 as allegedly omitting essential elements, because a label is not an essential element for the device or kit of claim 12. The degree of immunoreactivity can be measured by a variety of well established means, including immunoprecipitation (where the increase in absorbance is correlated with the concentration). (See, e.g., p. 13, line 16 – p. 14, line 4).

Claim 16 has been amended to delete the alternative language, and to insert that it is dependent on claim 12. Claims 18 and 19 have also been amended to insert the claim dependency.

The Applicants respectfully traverse the rejection to claim 20 as allegedly omitting essential elements. One of ordinary skill in the art would know how to detect immunoreactivity, with or without a label. The technical details of the detection of immunoreactivity need not to be fully disclosed in claim 20 to enable one of skill in the art to practice the claimed subject matter.

However, claims 1 and 20 have been amended to include correlations steps and to provide for a quantitative assay, since merely detecting a reaction would be of little use.

Rejections Under 35 U.S.C. § 102

Claims 1-3, 12, 14, 16-18, and 20 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 5,677,133 to Oberhardt. Claims 1-3, 12, 14, 16-18, and 20 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 5,601,911 to Oberhardt. Claims 1 and 4 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 6,210,906 to Kundu et al. Claims 16 and 18 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No.

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5,137,808 to Ullman et al. Claims 16 and 18 were rejected under 35 U.S.C. § 102 (b) as disclosed by U.S. Patent No. 5,559,041 to Kang, U.S. Patent No. 5,384,264 to Chen, or U.S. Patent No. 5,602,040 to May, et al. These rejections are respectfully traversed if applied to the amended claims.

The Claimed Invention

The claimed subject matter relates to a method and an assay device or kit to detect the levels of apolipoproteins in saliva. Although it was postulated that apolipoproteins were present in serum, it was not previously known that the levels could be correlated to serum levels, thereby making a non-invasive test using saliva a possibility. The Applicants demonstrated the correlation between levels of apolipoproteins in saliva and levels of HDL and LDL in serum. The independent claims have been amended to include the step, or additional components, required for determining the levels in saliva and correlating them with the levels of apolipoprotein in serum.

Oberhardt

Oberhardt (US 5,677,133), and Oberhardt (US 5,601,911) describe a method and a system of dry chemistry cascade immunoassay and affinity assay. The two Oberhardt patents suggest that the method and system can be used in an immunoassay for with whole blood, for small molecules, large molecules including apolipoproteins, important cardiovascular proteins, cellular elements or their surface antigenic or receptor molecules, HIV antigen, hormones, signal or structural elements out side or within cells, specific polynucleotides, and diagnostic tests for difficult biological samples including saliva, etc. (See columns 3 and 4 of US 5,601,911 and US

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5,677,133). Neither of the Oberhardt patents, however, specifically teaches the detection of the levels of apolipoproteins in saliva, nor, most importantly, that there is a correlation between the levels in saliva and the blood.

Neither of the Oberhardt patents provides the motivation to detect the levels of apolipoproteins in saliva. Neither of the Oberhardt patents teaches how the levels of apolipoproteins should be detected in saliva. Indeed, "saliva" is mentioned only once in the patents (Column 4, line 14 of and US 5,677,133, and Column 4, line 16 of US 5,601,911). Neither of the Oberhardt patents enables one of ordinary skill to detect the levels of apolipoproteins in saliva and extrapolate to the serum concentrations.

Kundu

Kundu describes specific antibodies to Apo A and methods to use the antibodies. Similar to the Oberhardt patents, Kundu does not teach why or how the levels of apolipoproteins should be detected in saliva, nor how to correlate the levels of the apolipoproteins in the saliva with the levels of the apolipoproteins in the serum, as defined by the amended claims.

Ullman and Kang

Ullman and Kang disclose a device for use in an immunoassay, but does not disclose a device which can be used to detect levels of apolipoprotein in saliva and correlate the levels with the levels in serum, as defined by the amended claims.

Rejections Under 35 U.S.C. § 103

Claims 5-7, 10, 11 and 13 were rejected under 35 U.S.C. § 103 as obvious over Oberhardt (US 5,677,133) or Oberhardt (US 5,601,911) in view of U.S. Patent No. 5,112,758 to

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Fellman. Claims 7-9, 15 and 19 were rejected as obvious over either Oberhardt in combination with Fisher, Diabetes Res. Clin. Practice 11(2) 117-119 (1991) (abstract only) and Coppo, J. Diabetic Complications 1(2), 58-60 (1987) (abstract only). These rejections are respectfully traversed if applied to the amended claims.

Oberhardt

Oberhardt is discussed above. As the examiner has acknowledged, neither Oberhardt discloses detecting apolipoproteins in saliva, nor normalizing that value to the concentrations in serum. None of the other references make up for these deficiencies.

Fellman

Fellman discloses a means for reducing the viscosity of a material such as saliva which contains mucopolysaccharides, using a cationic quaternary ammonium reagent. This method could indeed be used with applicants' claimed method. However, Fellman does not suggest detecting apolipoproteins in saliva, nor that the levels could be correlated with the levels in serum.

Fisher and Coppo

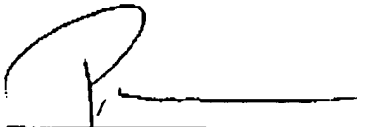
Fisher and Coppo provide assays for detecting albumin – one in saliva and one in urine. Neither, however, suggest detecting apolipoproteins in saliva, nor that the levels could be correlated with the levels in serum by measuring the values of the albumin.

Therefore none of the prior art, alone or in combination, discloses nor makes obvious the claimed methods and kit, as defined by the amended claims. Allowance of claims 1-20, as

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amended, and new claims 21-23, is therefore earnestly solicited.

Respectfully submitted,

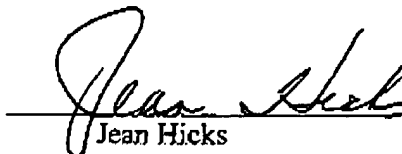


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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.



Jean Hicks

Date: November 19, 2001

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Marked Up Version of Amended Abstract

**METHOD AND DEVICE FOR DETECTION OF APO A, APO B
AND THE RATIO THEREOF IN SALIVA**

Abstract of the Invention

A method has been developed to detect the levels of apolipoproteins A-I and B in saliva, which is correlated with the levels of HDL and LDL in serum, respectively. In unstimulated saliva, the ration of Apo A to Apo B is correlated with the ration of HDL to LDL in serum. Albumin can be used to normalize the sample for dilution. The high degree of correlation in combination with a simple, quick test that can be performed at the site of collection provides a cost effective, patient friendly means to monitor an individual's risk of heart disease. In the preferred embodiment, saliva production is stimulated by means such as breath mint or tart solution (such as lemon) and the effect of dilution controlled by reference to albumin. ~~In the most preferred embodiment, the assay is an ELISA assay performed using Sorex laminated strip format as described in U.S. patent Nos. 5,710,009, 5,500,375, and 5,451,004. These strips are advantageous since they serve as the collection and assay device.~~

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Clean Version of Amended Abstract**METHOD AND DEVICE FOR DETECTION OF APO A, APO B
AND THE RATIO THEREOF IN SALIVA****Abstract of the Invention**

A method has been developed to detect the levels of apolipoproteins A-1 and B in saliva, which is correlated with the levels of HDL and LDL in serum, respectively. In unstimulated saliva, the ration of Apo A to Apo B is correlated with the ration of HDL to LDL in serum. Albumin can be used to normalize the sample for dilution. The high degree of correlation in combination with a simple, quick test that can be performed at the site of collection provides a cost effective, patient friendly means to monitor an individual's risk of heart disease. In the preferred embodiment, saliva production is stimulated by means such as breath mint or tart solution (such as lemon) and the effect of dilution controlled by reference to albumin.

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Marked Up Version of Amended Claims

1. (Amended) A method for [detection of] determining the level of an apolipoprotein in saliva comprising reacting the saliva with antibodies immunoreactive with the apolipoprotein in a quantitative assay, detecting the amount of immunoreactivity, and comparing the amount of immunoreactivity with standards to determine the level of apolipoproteins in the saliva.
2. The method of claim 1 wherein the apolipoprotein is selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.
3. The method of claim 2 wherein the apolipoprotein is selected from the group consisting of Apo A1 and Apo B.
4. (Amended) The method of claim 1 wherein the antibodies are labelled with a detectable [lable] label.
5. The method of claim 1 wherein the saliva is tested less than three hours following collection.
6. (Amended) The method of claim 1 wherein the saliva is prepared prior to testing to remove mucopolysaccharides from the saliva.
7. The method of claim 1 wherein the saliva is collected after stimulation.
8. The method of claim 1 further comprising determining the amount of albumin present in the saliva.
9. (Amended) The method of claim 8 further comprising normalizing the amount of the apoplipoprotein to the amount of albumin present in the saliva of the individual from whom the saliva was obtained.

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10. The method of claim 1 wherein the saliva is collected into a device which filters out mucopolysaccharides and comprises antibodies immunoreactive with one or more apolipoproteins.
11. The method of claim 10 wherein the apolipoprotein is either Apo A1 or Apo B.
12. An assay device or kit for determining the amount of apolipoprotein in a saliva sample comprising means for collection of saliva and antibodies immunoreactive with an apolipoprotein for use in a quantitative assay, and means for comparing the levels of the apolipoproteins in the saliva with the levels in serum.
13. (amended) The assay device or kit of claim 12 comprising filter means for removal of [mucopolysaccharide] mucopolysaccharides from the saliva.
14. The assay device or kit of claim 12 wherein the antibodies are reactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.
15. The assay device or kit of claim 12 further comprising antibodies immunoreactive with albumin.
16. (Amended) The assay device or kit of claim 12 wherein the antibodies are [contained on or] immobilized on a solid support.
17. The assay device or kit of claim 16 comprising reagents for detection of complexes between the apolipoprotein and the antibodies.
18. (Amended) The assay device or kit of claim 12 comprising a strip or dipstick.

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19. (Amended) The assay device or kit of claim 15 comprising as separate reagents antibodies to [an] the apolipoprotein and antibodies to albumin.
20. (Amended) A method for quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease comprising reacting a saliva sample with antibodies specifically immunoreactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof in a quantitative assay.
21. (New) The method of claim 1 further comprising,
 determining the correlation between the levels of HDL and/or LDL and the levels of apoprolipoproteins in serum, and
 determining the levels of HDL and/or LDL in the serum, based on the measurements of the levels of the apolipoproteins in the saliva.
22. (New) The method of claim 20 comprising quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease by reacting a saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof, and
 correlating the levels of at least one apolipoprotein in the saliva with the levels in serum associated with the presence of lipid disorders or risk of cardiovascular disease.

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23. (New) The method of claim 20 wherein the measurements of the apolipoproteins in serum are normalized against the level of albumin in the saliva as compared to the level of albumin in serum from the individual.

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Clean Version of Amended Claims

1. (Amended) A method for determining the level of an apolipoprotein in saliva comprising reacting the saliva with antibodies immunoreactive with the apolipoprotein in a quantitative assay, detecting the amount of immunoreactivity, and comparing the amount of immunoreactivity with standards to determine the level of apolipoproteins in the saliva.
2. The method of claim 1 wherein the apolipoprotein is selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.
3. The method of claim 2 wherein the apolipoprotein is selected from the group consisting of Apo A1 and Apo B.
4. (Amended) The method of claim 1 wherein the antibodies are labelled with a detectable label.
5. The method of claim 1 wherein the saliva is tested less than three hours following collection.
6. (Amended) The method of claim 1 wherein the saliva is prepared prior to testing to remove mucopolysaccharides from the saliva.
7. The method of claim 1 wherein the saliva is collected after stimulation.
8. The method of claim 1 further comprising determining the amount of albumin present in the saliva.
9. (Amended) The method of claim 8 further comprising normalizing the amount of the apolipoprotein to the amount of albumin present in the saliva of the individual from whom the saliva was obtained.

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10. The method of claim 1 wherein the saliva is collected into a device which filters out mucopolysaccharides and comprises antibodies immunoreactive with one or more apolipoproteins.
11. The method of claim 10 wherein the apolipoprotein is either Apo A1 or Apo B.
12. An assay device or kit for determining the amount of apolipoprotein in a saliva sample comprising means for collection of saliva and antibodies immunoreactive with an apolipoprotein for use in a quantitative assay, and means for comparing the levels of the apolipoproteins in the saliva with the levels in serum.
13. (amended) The assay device or kit of claim 12 comprising filter means for removal of mucopolysaccharides from the saliva.
14. The assay device or kit of claim 12 wherein the antibodies are reactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof.
15. The assay device or kit of claim 12 further comprising antibodies immunoreactive with albumin.
16. (Amended) The assay device or kit of claim 12 wherein the antibodies are immobilized on a solid support.
17. The assay device or kit of claim 16 comprising reagents for detection of complexes between the apolipoprotein and the antibodies.
18. (Amended) The assay device or kit of claim 12 comprising a strip or dipstick.

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19. (Amended) The assay device or kit of claim 15 comprising as separate reagents antibodies to [an] the apolipoprotein and antibodies to albumin.
20. (Amended) A method for quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease comprising reacting a saliva sample with antibodies specifically immunoreactive with apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof in a quantitative assay.
21. (New) The method of claim 1 further comprising,
determining the correlation between the levels of HDL and/or LDL and the levels of apoprolipoproteins in serum, and
determining the levels of HDL and/or LDL in the serum, based on the measurements of the levels of the apolipoproteins in the saliva.
22. (New) The method of claim 20 comprising quantitating the amount of lipoprotein or cholesterol in saliva or determining the presence of lipid disorders or risk of cardiovascular disease by reacting a saliva sample with antibodies specifically immunoreactive with an apolipoprotein selected from the group consisting of Apo A, Apo B, Apo C, Apo E, and components thereof, and
correlating the levels of at least one apolipoprotein in the saliva with the levels in serum associated with the presence of lipid disorders or risk of cardiovascular disease.

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23. (New) The method of claim 20 wherein the measurements of the apolipoproteins in serum are normalized against the level of albumin in the saliva as compared to the level of albumin in serum from the individual.

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